DETAILED ACTION

This application is a national stage entry of PCT/JP04/18765, filed on 12/9/2004.

Priority

A claim has been made for foreign priority to 2003-410432, filed on 12/9/2003.

Response to Remarks

1. Applicant's arguments, filed 2/10/2010, with respect to the rejection of claims 2-5, 9-12, and 16 under 35 USC 112, first paragraph, have been fully considered and are persuasive. The claims have been amended to remove "preventing"; therefore, the rejection under 35 USC 112, first paragraph has been withdrawn. Claims 2-5 and 16 have been cancelled by the Applicants, and the rejection of these claims is considered moot.

2. Applicant's arguments filed 2/10/2010, regarding the rejection of claims 2-5, 9-12, and 16 under 35 USC 103(a) have been fully considered but they are not persuasive. In the reply filed on 2/10/2010, the claims were amended to recite treatment of an impairment of higher brain function caused by brain injury due to head trauma. Due to this amendment, the Applicants have argued that as the prior art does not teach administration of (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine for treating head trauma, the claims are non-obvious over the prior art. The Applicants have also stated that hypoxia-ischemia is not related to head trauma. The examiner respectfully disagrees. An updated search of the prior art as it applied to the amended claim set provides support that brain ischemia is a common occurrence in patients who have suffered traumatic head injuries. As Shimada et. al. teaches that (E)-8-(3,4-

dimethoxystyryl)-1,3-diethyl-7-methylxanthine (also known commercially as KW 6002) is effective for treating neurodegenerative disorders and brain ischemia, and Ikeda et. al. teaches that ischemic brain damage results in impairments in learning and memory, one of ordinary skill in the art would have been motivated to treat impairments in learning and memory with (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine. Additionally, as the prior art teaches that traumatic head injuries are often associated with brain ischemia, it would have been prima facie obvious for one of ordinary skill in the art to treat impairments of higher brain function caused by traumatic head injury with (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine, because it is known that (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine effectively treats brain ischemia, and brain ischemia is associated with impairments in learning and memory. A modified rejection has been made in view of the claim amendments, which will be discussed in detail in the office action.

3. The Applicants have argued that the rejections for obviousness type double patenting over the claims of US Patent No. 7,115,614, and US Patent No. 6,727,259 should be withdrawn due to the claim amendments. This argument is not found persuasive, as the claim of US Patent No. 7,115,614 is drawn to treatment of brain ischemia with (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine. As brain ischemia is observed with traumatic head injuries, both sets of claims are obvious over each other. Additionally, the claims of US Patent No. 6,727,259 are drawn to treatment of neurodegeneration comprising administration of (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine. An updated search of the prior art provides support that

neurodegeneration is also associated with traumatic head injury. As such, the rejections for obviousness type double patenting are maintained. Modified rejections have been made in view of the claim amendments, which will be discussed in detail further in the office action. Accordingly, this action is made FINAL. Currently, claims 9-12 are pending.

4. Claims 9-12 were examined.

5. Claims 9-12 are rejected.

Claim Rejections-35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimada et. al., EP 1016407 patent publication, in view of Manley et. al., *Archives Surg.*, **136**, pp. 1118-1123, (2001), and further in view of Ikeda et. al., *Behavioral Brain Research*, **118**, pp. 17-25. Shimada et. al. and Ikeda et. al. were both previously of record.

The claims are directed to a method of treating an impairment of higher brain function caused by brain injury due to head trauma, in which the impairment affects memory, thinking, recognition, action, or learning, comprising administration of (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine, or KW 6002, to a patient in need thereof.

Shimada et. al. teaches that xanthine compounds such as KW 6002 are effective for treating neurodegenerative disorders, including Alzheimer's disease, propagating spongy brain fever, brain ischemia, and others (p. 2, paragraph [0001]; p. 5, Table 1, compound No. 1, lines 5-10, and lines 35-40; p. 8, paragraph [0028]).

While Shimada et. al. teaches that KW 6002 is effective for treating neurodegenerative disorders and brain ischemia, it is not explicitly taught as a treatment for higher brain dysfunctions such as memory, learning, and other cognitive skills.

Shimada et. al. does not explicitly teach treatment of higher brain function impairments due to brain injury from head trauma.

Manley et. al. teaches that brain injury is a significant cause of death after head trauma (p. 1118, 1st paragraph). Hypoxia and ischemia can occur as a result of a traumatic head injury (p. 1118, 1st paragraph). Cerebral blood flow can be considerably lessened after a traumatic head injury, causing hypoxia of the brain, and ischemic brain damage has been observed at autopsy in up to 90% of patients who had suffered traumatic head injuries (p. 1121, left column, 3rd paragraph).

It would have been prima facie obvious to one of ordinary skill in the art, at the time of the invention, to treat patients afflicted with brain ischemia due to brain injury from head trauma with KW-6002, because Shimada et. al. teaches that KW-6002 is effective for treating brain ischemia, and Manley et. al. teaches that brain ischemia is commonly observed in patients who have suffered a traumatic head injury. As it is taught that brain ischemia occurs in many patients who have been afflicted with a traumatic head injury, one of ordinary skill in the art would have expected success in treating such patients by administration of KW-6002, given the effectiveness of treating brain ischemia with this compound.

Shimada et. al. nor Manley et. al. explicitly teach that brain ischemia is associated with impairments in higher brain function, such as impairments in learning, memory, recognition, etc.

Ikeda et. al. teaches that ischemic brain damage results in considerable long lasting learning and memory impairment (Abstract). Ikeda et. al. teaches that in subjects

who were afflicted with cerebral ischemia, learning of new tasks and spatial cognition were impaired (p. 20, right column, full paragraphs 2-3). It is also taught that attention deficits were observed in these subjects, and that learning abnormalities and impairments in long-term memory and reference memory were apparent (p. 23, right column, first full paragraph; p. 24, right column, last two paragraphs).

Shimada et. al. teaches that KW 6002 is effective in treating neurodegenerative diseases and conditions, including brain ischemia, and Ikeda et. al. teaches that brain ischemia results in pronounced deficits involving learning and memory. It would have been prima facie obvious for one of ordinary skill in the art, at the time of the invention, to treat a patient suffering from learning and memory impairments with KW 6002, because it is taught that this agent is effective for treating neurodegenerative conditions such as brain ischemia, which is associated with learning and memory impairments. Therefore, one of ordinary skill in the art would have expected success in treating learning and memory impairments with KW 6002, because the prior art teaches that this compound is effective in treating a condition which is associated with these impairments. Additionally, amnesia is defined as a partial or total loss of memory (http://www.credoreference.com/search.do?query=amnesia&subject=ali&scope=title&title=502&view=facet). As Ikeda et. al. teaches that memory impairment, and therefore amnesia, is associated with brain ischemia, it would have been prima facie obvious for one of ordinary skill in the art to administer KW 6002 to treat amnesia. Furthermore, as Manley et. al. teaches that brain ischemia is commonly observed in patients who have experienced a traumatic head injury, it would have been obvious to administer KW-6002

to treat impairments of higher brain function in such patients, because Shimada et. al. teaches that KW-6002 is administered to treat brain ischemia, and brain ischemia is associated with learning and memory impairments.

Claim Rejections-Obviousness Type Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 9-12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,115,614 in view of Ikeda et. al., *Behavioral Brain Res.*, **118**, pp. 17-25, and Manley et. al., *Arch. Surg.*, **136**, pp. 1118-1123, (2001).

The claims are drawn to treatment of higher brain cognitive impairments involving learning and memory, caused by brain injury due to head trauma, with the elected compound KW 6002. Claim 1 of the US Patent No. 7,115,614 is drawn to treatment of

brain ischemia, comprising administration of KW 6002. Ikeda et. al. teaches that brain ischemia is associated with impairments in learning and memory (p. 23, right column, first full paragraph; p. 24, right column, last two paragraphs), and Manley et. al. teaches that brain ischemia is common in patients who have suffered a traumatic head injury (p. 1118, 1st paragraph; p. 1121, left column, 3rd paragraph). Therefore, as impairments in learning and memory are associated with brain ischemia, and brain ischemia is commonly observed as a result of traumatic head injury, one of ordinary skill in the art would have expected that in treating brain ischemia, the learning and memory impairments associated with brain ischemia as a result of brain injury from head trauma would also have been treated with KW 6002. Therefore, the claims are not patentably distinct from each other.

12. Claims 9-12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,727,259 in view of Ikonomidou et. al., *Metabolic Brain Disease*, 11(2), pp. 125-141.

The claims are drawn to treatment of higher brain cognitive impairments involving learning and memory, caused by brain injury due to head trauma, with the elected compound KW 6002. Claims 1-3 of the US Patent No. 6,727,259 are drawn to treatment and inhibition of neurodegeneration and neurodegenerative disorders, comprising administration of KW 6002. It is well known in the art that a variety of neurodegenerative disorders, such as Alzheimer's disease are marked by a progressive decline in cognitive

function, including memory and learning (http://www.merck.com/mmhe/sec06/ch083/ch083c.html#sec06-ch083-ch083c-522). Ikonomidou et. al. teaches that neurodegeneration is a serious consequence of traumatic head injury (Abstract; p. 126, 2nd and 3rd full paragraphs;. p. 129, 2nd full paragraph; p. 131, 2nd full paragraph). Therefore, as the instant claims are drawn to treating impairments in memory and learning caused by brain injury from traumatic head injury, and these impairments are associated with neurodegenerative conditions such as Alzheimer's disease, both sets of claims are not patentably distinct from each other. Additionally, as Ikonomidou et. al. teaches that neurodegeneration is observed in subjects who have experienced traumatic head injury, both claim sets are obvious over each other.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

14. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/
Primary Examiner, Art Unit 1627

S.P.